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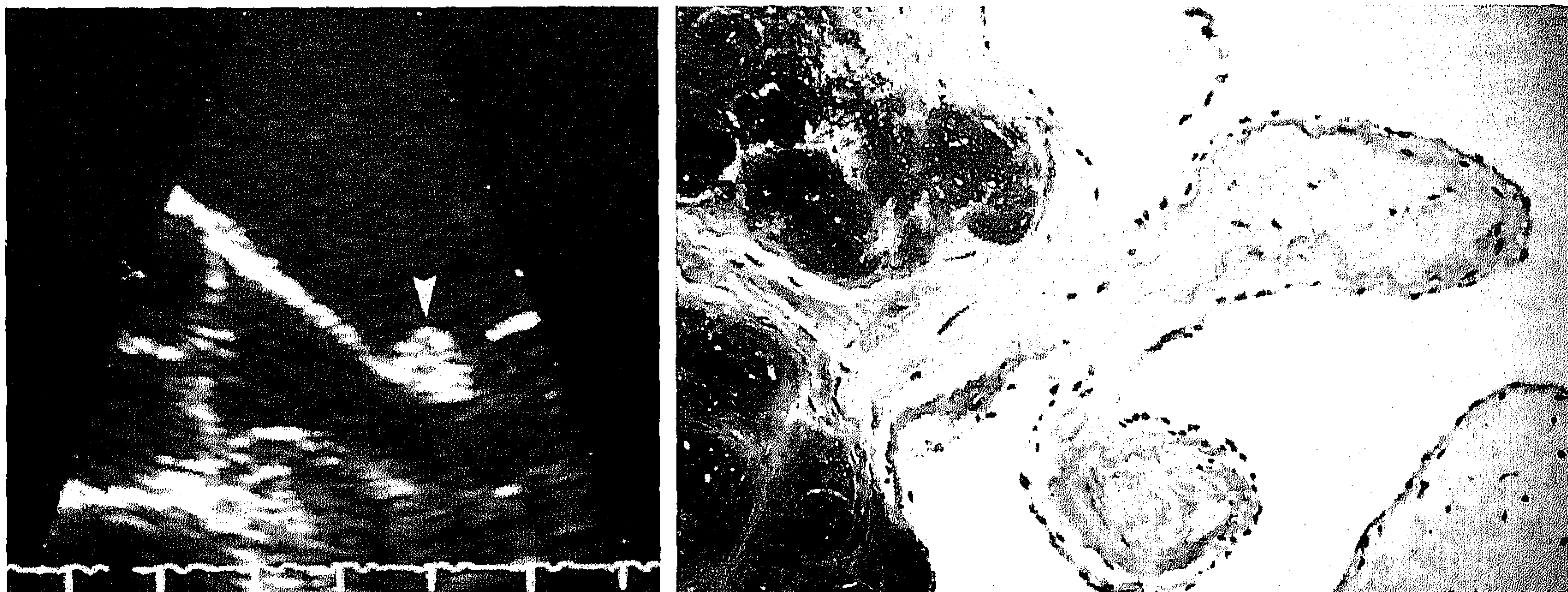


Fig 2. Left, Transesophageal echocardiograph of left atrium demonstrating small papilliform lesion on the atrial surface of the mitral valve (arrowhead). Right, Histology of lesion excised from mitral valve. Elastin stain,  $\times 25$ .

has been advocated, although postmortem series suggest that fibroelastoma is usually an incidental finding.

TEE is superior to TTE or physical examination for the detection of potential cardioembolic sources.<sup>4,5</sup> As with this case, normal TTE with potentially emboligenic abnormalities on TEE has been reported.<sup>6,7</sup> Limited availability of TEE and the uncertain management of many abnormalities demonstrated only by this modality prevent its routine use after stroke.

Brief high-intensity signals on TCD are thought to represent emboli. Spectral analysis may distinguish air from platelet or fibrin thrombi.<sup>8</sup> The number of signals correlates with the degree of neuropsychological dysfunction evident after cardiopulmonary bypass procedures<sup>9</sup> and may differentiate lacunar strokes (thought to result from small-vessel occlusion) and other stroke types.<sup>10</sup> HITS on TCD may represent continuing subclinical embolism.

The demonstration of bilateral embolic signals in this case contributed to the clinical decision to undertake TEE despite normal TTE results. The spectral pattern of the emboli suggested solid material, but thrombi could not be distinguished from tumor fragments. Difficulties in determining the nature of the embolic material impair the clinical usefulness of TCD detection of HITS at present. However, this case demonstrates that embolic signal monitoring by TCD may be a useful adjunct in the investigation of patients with a clinical suspicion of an embolic source and particularly may prompt TEE if bilateral HITS are observed.

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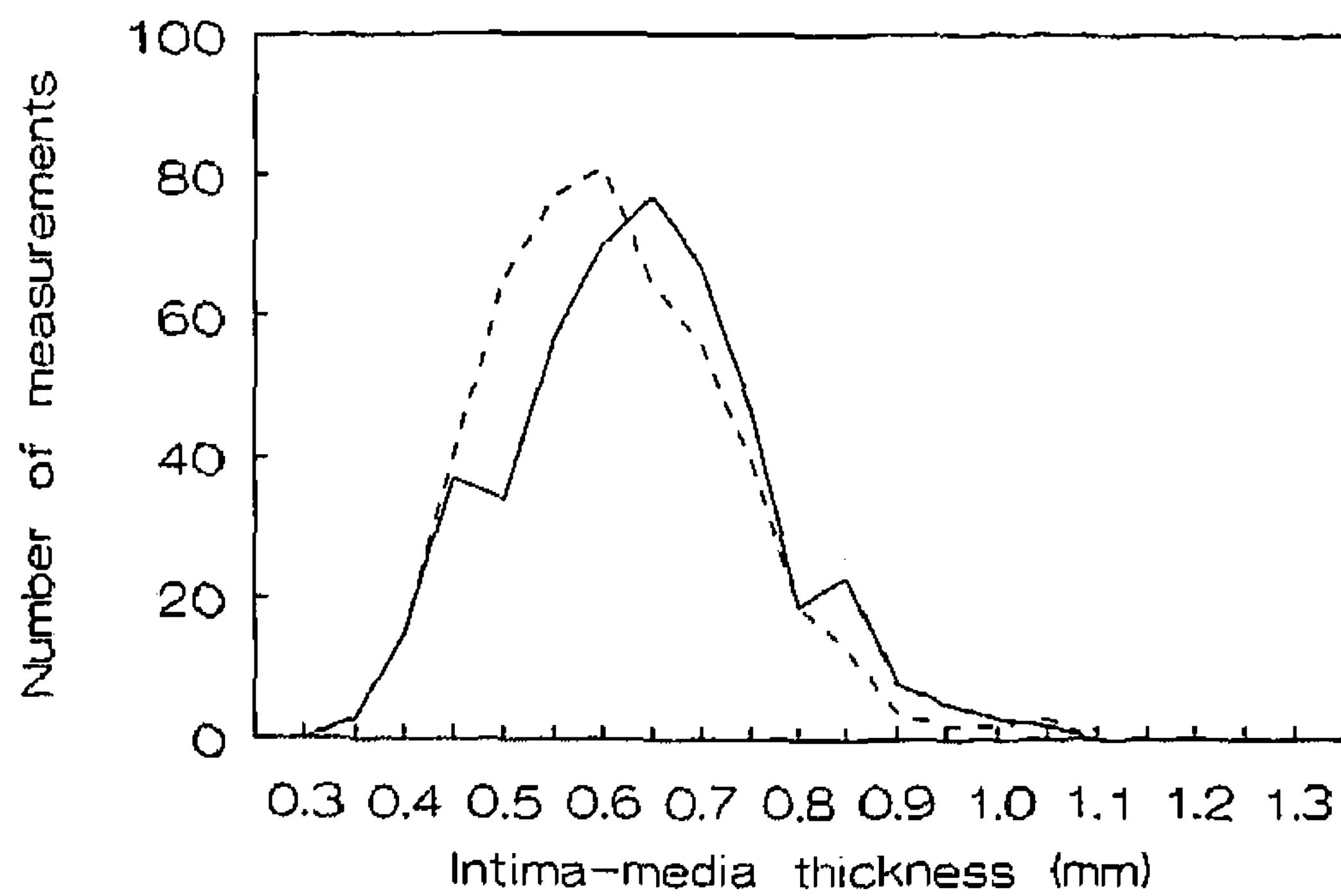
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### Evaluation of the Presence of Premature Atherosclerosis in Adults With Heterozygosity for Cystathionine- $\beta$ -Synthase Deficiency

To the Editor:

Premature atherosclerosis is a key clinical feature of homozygous homocystinuria, an autosomal recessively inherited condition characterized by hyperhomocysteinemia.<sup>1</sup> In homocystinuria, hyperhomocysteinemia is in most cases due to the low activity of cystathionine- $\beta$ -synthase (CS), which catalyzes the conversion of homocysteine to cystathionine. In some patients, hyperhomocysteinemia is caused by a defect in the remethylation of homocysteine to methionine because of a deficiency of methionine synthase or methylenetetrahydrofolate reductase. Relatives of patients with homozygous homocystinuria who are obligate heterozygotes have hyperhomocysteinemia. Since homocysteine may be involved in atherogenesis,<sup>2</sup> these subjects may be at increased risk for premature atherosclerosis. Because previous studies on manifestations of cardiovascular disease have yielded conflicting results,<sup>3-5</sup> we studied the prevalence of carotid and femoral atherosclerosis by measuring intima-media thickness (IMT) and ankle-brachial index (ABI) in enzymatically proven heterozygous relatives of patients with homozygous homocystinuria due to CS deficiency.





Distribution of intima-media thickness in the group of subjects younger than 50 years heterozygous for cystathionine- $\beta$ -synthase deficiency (solid line) and control subjects (dashed line).

Twenty-three subjects (14 parents and 9 siblings) were recruited from seven families. Three parents were not available (2 because of family circumstances, and 1 refused to participate), and 1 young sibling (10 years) was excluded. Of the remaining 19 members, we concentrated on the 13 subjects (5 males and 8 females) younger than 50 years of age because the aim was to study premature atherosclerosis. Mean age was 33.3 (range, 18 to 50) years. The control group consisted of 12 healthy subjects with normal methionine loading test results. Blood pressure, plasma creatinine, and fasting plasma lipids were similar in both groups. There were more smokers in the control group (9) than in the heterozygote group (2,  $P=.015$ ).

Clinical manifestations of coronary, cerebral, or peripheral artery disease were evaluated by medical history and documentation. Since lens luxation occurs frequently in patients with homozygous homocystinuria, the heterozygous relatives were examined ophthalmologically (with fundoscopy and photography).

CS activity was measured in cultured skin fibroblasts by the radioisotopic method of Mudd et al<sup>6</sup> in assays without and with pyridoxal phosphate. Subjects were defined as heterozygotes if CS activity was below the lower limit of normal. In vivo homocysteine metabolism was assessed in an oral methionine loading test. Subjects ingested 100 mg/kg body weight of L-methionine after an overnight fast, and blood was sampled before and 6 hours after methionine ingestion. Plasma total homocysteine was measured by the method of Araki and Sako.<sup>7</sup> Test results were abnormal if the basal homocysteine level was  $>16.3 \mu\text{mol/L}$  in women and  $>18.8 \mu\text{mol/L}$  in men and/or if the increase was  $>42.3 \mu\text{mol/L}$  after loading in both sexes. Plasma concentrations of the cofactors pyridoxine, folic acid, and cyanocobalamin were determined before loading. In relatives, a low enzyme activity was minimally required as proof of heterozygosity. ABI was determined at rest and after exercise; ABI  $<0.94$  was considered indicative of atherosclerotic changes. IMT was measured in segments of distal common carotid, carotid bulb, proximal internal carotid, common femoral, and superficial femoral artery from both sides. IMT was defined as the average distance between lumen-intima and media-adventitia interfaces of each arterial wall segment.

The IMT measurements (mean  $\pm$  SD) were normally distributed, and thus the results of heterozygote and control subjects were compared with the Student's  $t$  test. Data for all measured segments (0.05-mm contingents) were pooled, and a frequency distribution was calculated. Level of significance was .05.

None of the subjects had clinical evidence of cerebral, coronary, or peripheral arterial disease. Ocular abnormalities associated with homocystinuria were not found. All 13 relatives had low unstimulated and stimulated CS activities and were considered heterozygotes. In 11 of the 13 heterozygous subjects, results of the

methionine loading test were abnormal. (Although the results were within the normal range in two subjects from one family, these subjects were considered heterozygotes because of low CS activity.) Plasma concentrations of cofactors were all within the normal range except for one marginally lowered cobalamin value.

One heterozygous subject had a marginally low ABI (0.93) in one leg. Doppler measurements did not reveal stenoses in the heterozygote group. The exercise test did not reveal abnormal decreases in ABI. Mean IMT values were similar in the heterozygous ( $0.59 \pm 0.13$  mm; median, 0.58 mm) and control groups ( $0.59 \pm 0.11$  mm; median, 0.58 mm;  $P=.8$ ), with an almost identical IMT frequency distribution (Figure). IMT was also similar for both groups for each of the five arterial segments.

The absence of changes in the vascular wall of subjects who have been exposed to a presumed atherogenic factor may be explained in several ways. First, it may be that the relatives were too young to have developed structural vascular changes. In one study, heterozygous subjects with an increased carotid IMT were significantly older than subjects with a normal IMT.<sup>5</sup> The mean  $\pm$  SD age of the patients in the study who showed lower mean ABI and higher frequency of Doppler abnormalities in heterozygote subjects compared with control subjects was  $46 \pm 12$  years, indicating that if normally distributed there would be the same number of subjects older and younger than 46 years. In the study of Malinow et al,<sup>8</sup> the asymptomatic subjects who had an increased IMT with high plasma homocysteine levels were between 45 and 64 years of age. However, patients of comparable or younger age than our subjects with other atherogenic conditions, such as insulin-dependent diabetes mellitus or familial hypercholesterolemia,<sup>9-12</sup> have been shown to have an increased IMT. Second, although cross-sectional and prospective studies have demonstrated that hyperhomocysteinemia is associated with an increased risk of premature atherosclerosis, these are not heterozygous for CS deficiency, and in addition multiple risk factors may be present and interact.<sup>13</sup> A high frequency of decreased rate of remethylation with decreased activity of the thermolabile fraction of methylene tetrahydrofolate reductase has been detected in these patient groups.<sup>14</sup> Third, hyperhomocysteinemia may affect the coagulation cascade more than the vascular wall.<sup>15-17</sup> Our results do not support rigorous implementation of extensive vascular assessment of subjects who are heterozygous for CS deficiency and whose homozygous relatives have symptomatic disease.

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